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Association between early dexmedetomidine administration and outcomes in critically ill patients with depressive disorders

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Abstract

Background Fewer studies have focused on sedative strategies for critically ill patients with depression. Previous research has suggested that dexmedetomidine may benefit patients with depressive disorders. This study investigated the association between early dexmedetomidine use and clinical outcomes in a cohort of critically ill patients with depressive disorders, based on real-world electronic health records.

Methods Patients diagnosed with depressive disorders in Intensive Care Unit (ICU) were identified from the Medical Information Mart for Intensive Care (MIMIC)-IV database. Early dexmedetomidine exposure was defined as continuous intravenous infusion for at least 1 hour within the first 48 hours after ICU admission. Propensity score matching was performed to balance baseline characteristics between patients with and without early dexmedetomidine exposure. Logistic regression and Cox regression were employed to evaluate the associations of early dexmedetomidine use with in-hospital mortality and 30-day mortality, respectively.

Results The analysis included 3936 patients. Following propensity score matching, 353 pairs were formed between the dexmedetomidine and non-dexmedetomidine groups. After propensity score matching, early dexmedetomidine use was significantly associated with lower 30-day mortality (HR = 0.577, 95% CI: 0.371-0.898, P = 0.015) and in-hospital mortality (OR = 0.465, 95% CI: 0.274-0.791, P=0.005). Subgroup analyses indicated that the association was consistent across various clinical strata, including age, sepsis, SOFA scores, GCS scores, delirium, mechanical ventilation and antidepressant use (P for interaction> 0.05).

Conclusions Early dexmedetomidine administration was associated with lower mortality in ICU patients with pre-existing depressive disorders. This association between dexmedetomidine and improved outcomes appeared robust across various clinical subgroups. Randomized controlled trials are needed to validate these findings.

Keywords Dexmedetomidine; Depressive Disorders; Critical Care; Mortality

Background

Depressive disorders are common mental health conditions that affects individuals across all age groups, with an estimated global prevalence of over 300 million people worldwide, imposing a substantial burden on healthcare systems[1]. Notably, preexisting mental illness has been independently associated with adverse clinical outcomes, including higher readmission rates, prolonged hospital stays, and increased surgical complications following operative procedures or trauma[2,3]. In ICU settings, patients often need respiratory and circulatory support alongside invasive therapeutic interventions, which may induce significant discomfort and distress. These stressors can

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precipitate anxiety and potentially exacerbate pre-existing depressive conditions. If a carefully chosen sedative could be used in critical care, this would help protect mental health, especially for patients with depression, by adjusting medications to prevent symptoms from worsening while keeping treatment effective.

Dexmedetomidine, a highly selective alpha-2 receptor agonist, has been widely used in critical care, offering sedation, analgesia, and anxiolysis without suppressing respiratory drive[4]. Growing preclinical researches have suggested its potential to modulate neurobiological pathways implicated in depression[5-7]. Clinical studies also suggest that dexmedetomidine is linked to a lower incidence of postpartum depression and improved sleep architecture- an essential consideration for ICU patients who frequently experience sleep disruption[8,9]. Furthermore, increasing evidence suggest that dexmedetomidine can suppress inflammatory response in sepsis and offers organ protective effects, which was also an important part of critical care[10,11].

However, evidence remains limited regarding the potential clinical associations of specific sedation protocols in ICU patients with pre-existing depression. This study aims to investigate the relationship between dexmedetomidine and clinical outcomes in ICU patients with depression, which may provide more evidence to guide the sedation. We explored the association of early dexmedetomidine use within 48h in ICU on in-hospital mortality and 30-day mortality.

Materials and methods

Source of data

This retrospective analysis leveraged data from the Multiparameter Intelligent Monitoring in Intensive Care Database IV (MIMIC-IV 3.0), a public repository comprising de-identified electronic health records for more than 70000 ICU patients at Beth Israel Deaconess Medical Center (BIDMC). The Institutional Review Boards of BIDMC and the Massachusetts Institute of Technology (MIT) approved the study protocol and waived the requirement for informed consent. Access to the database was authorized for the primary investigator (certification number: 12164196).

Population selection criteria

This study enrolled adult patients (over 18 years of age) with a diagnosis of major depressive disorder, as defined by ICD-9 and ICD-10 codes in the MIMIC-IV database. Patients aged 18 years or younger, those with more than 5% missing data among the potential mortality risk factors, and those who died within the first 48 hours after ICU admission were excluded. Only the data of each patient's first ICU admission were used in this study. Patients in the dexmedetomidine group were defined as those receiving a continuous intravenous infusion for at least 1 hour within the first 48 hours of ICU admission, with the remaining patients making up the non-dexmedetomidine group.

Data extraction and missing data management

We extracted clinical information from the initial 48 hours of ICU admission, encompassing demographics (age, gender), comorbidities, SOFA (Sequential Organ Failure Assessment) score, CAM-ICU (Confusion Assessment Method for the ICU) assessment, RASS (Richmond Agitation-Sedation Scale) score, vital signs (mean arterial pressure), laboratory results, and the use of renal replacement therapy and mechanical ventilation. All included variables contained fewer than 5% missing values. Continuous variables with less than 5% missing data were imputed using multiple imputation by chained equations (MICE), with five imputed datasets generated. All other study variables had no missing data and therefore required no imputation. Sepsis was identified according to the Sepsis-3 criteria using the derived sepsis3 data in the MIMIC-IV database. Information on dexmedetomidine, propofol, midazolam and anti-depression drugs administration (including Selective Serotonin Reuptake Inhibitors, Serotonin and Norepinephrine Reuptake Inhibitors, Tricyclic Antidepressants and Monoamine Oxidase Inhibitors), was also collected. Assessment of Delirium using CAM-ICU Delirium status was identified based on the CAM-ICU flowsheets recorded in the MIMIC-IV chartevents table. We extracted data from the following four clinical features: feature 1 (Acute Change or Fluctuating Course), feature 2 (Inattention), feature 3 (Altered Level of Consciousness), feature 4 (Disorganized Thinking). A patient was defined as delirium-positive if they simultaneously manifested Features 1 and 2, plus either Feature 3 or Feature 4. For our analysis, we categorized patients as having delirium if they had at least one "positive" CAM-ICU assessment during the initial 48 hours of their ICU stay.

Outcomes

The primary outcome was defined as in-hospital mortality, while secondary outcomes comprised the length of ICU stay and 30-day mortality following ICU admission.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range [IQR]) and compared using the Student's t-test or the Mann–Whitney U test, as appropriate based on the Shapiro-Wilk normality test. Categorical variables, presented as numbers (percentages), were assessed with the chi-square test. Propensity scores were estimated from a multivariable logistic regression model with early dexmedetomidine exposure as the dependent variable. The model included 18 prespecified covariates, all ascertained within the first 48 hours of ICU admission: sex, age, body weight, mean arterial pressure, platelet count, serum creatinine, SOFA score, chronic kidney disease, severe liver disease, malignant cancer, sepsis, delirium, mechanical ventilation, vasopressor use, renal replacement therapy, antidepressant use, propofol use and midazolam use. The study performed propensity score matching (PSM) to control for potential confounding. Propensity scores were calculated by employing a nearest neighbor matching algorithm on the logit of the propensity score without replacement (1:1 match, caliper 0.02). No variable selection was applied. The degree of PSM was evaluated by means of standardized mean difference (SMDs) (Table 1), with SMD values less than 0.1 considered acceptable. For variables that remained slightly imbalanced ($0.1 < SMD < 0.2$) after matching, further adjustment was performed in the subsequent multivariable regression models to ensure the robustness of the results. Propensity score distribution plots was used to confirm clinical exchangeability, and Love plot (Standardized Mean Difference plot) was used to graphically present the balance of all baseline covariates before and after matching.

The association of dexmedetomidine with clinical outcomes was analyzed using multiple statistical approaches before and after PSM. For 30-day mortality, a Cox proportional hazards model was employed (variables were selected using a backward stepwise elimination approach, with a removal criterion of $P > 0.10$). The proportional hazards assumption was formally verified using Schoenfeld residuals. E-values were calculated for the observed Hazard Ratios (HRs). In-hospital mortality and ICU length of stay were analyzed using multivariable logistic and linear regression, respectively. In the matched cohort, survival curves were estimated using the Kaplan-Meier method and compared via the log-rank test. Sensitivity analyses included overlap weighting in the overall cohort and Cox regression after excluding patients in the initial non-dexmedetomidine group who subsequently received dexmedetomidine after 48 hours of ICU admission.

Subgroup analyses were performed in the post-PSM population to assess the consistency of the association between dexmedetomidine and 30-day mortality across predefined subgroup according to age, SOFA scores, GCS scores, Antidepression drug use, Sepsis, Mechanical ventilation, Delirium. Interactions were assessed by including interaction terms in the Cox models.

All statistical analyses were conducted using R (version 4.2.2, R Foundation for Statistical Computing), with a $p < 0.05$ defining statistical significance.

Results

Basic characteristics

This study initially enrolled 28,083 patients diagnosed with depression. After excluding patients meeting exclusion criteria, 3,936 patients were included (Fig.1). A total of 360 patients were administered dexmedetomidine within the first 48 hours after ICU admission (dexmedetomidine group). The remaining 3,576 individuals did not receive the drug (non-dexmedetomidine group). Following propensity score matching, 353 pairs were formed between the dexmedetomidine and non-dexmedetomidine groups.

Significant differences existed between the non-dexmedetomidine and dexmedetomidine groups regarding gender composition and age (Table 1). Patients receiving dexmedetomidine were more likely to be male (55.6% vs. 44.6%), and were younger (58.5 ± 16.9 vs. 62.7 ± 16.5). The dexmedetomidine group also had lower mean blood pressure (79.0 ± 10.0 vs. 81.9 ± 11.4), lower platelet levels (182.5 vs. 210), and higher white blood cell counts (11.7 vs. 10.5) after ICU admission compared to those without dexmedetomidine administration. The prevalence of cancer (6.1% vs. 10.5%) or renal disease (12.5% vs. 17.2%) was lower, while the prevalence of sepsis (58.3% vs. 44.4%) was higher, among patients receiving dexmedetomidine. The use of mechanical ventilation (81.9% vs. 32.3%) and vasoactive drugs (36.7% vs. 17.8%) was more common in the dexmedetomidine group. Moreover, the prevalence of delirium was higher in the dexmedetomidine group (60.8% vs. 27.0%). The percentages of patients receiving propofol or midazolam were higher in the dexmedetomidine group. The dexmedetomidine group had significantly higher SOFA score than the non-dexmedetomidine group (5 vs. 3). Although the SMD of midazolam use (14.3%) still slightly imbalanced after PSM, further adjustment was performed in the subsequent multivariable regression models. Figure 2 shows the Propensity score distribution plots before and after matching. As shown in the Love plot in Figure 3, matching substantially reduced imbalance.

Table 1 Baseline characteristics between groups.

Variable	Unmatched patients		P	Propensity-score-matched patients		SMD (%)
	Non-dexmedetomidine n = 3576	Dexmedetomidine n = 360		Non-dexmedetomidine n = 353	Dexmedetomidine n = 353	
Baseline characteristics						
Male, n (%)	1593 (44.6%)	200 (55.6%)	<0.001	193 (54.7%)	195 (55.2%)	1.1
Age, mean ± SD, year	62.7 ± 16.5	58.5 ± 16.9	<0.001	59.9 ± 17.1	58.8 ± 16.7	6.4
Weight, mean ± SD, kg	82.0 ± 23.7	84.4 ± 23.8	0.095	84.7 ± 23.0	84.3 ± 24.0	1.4
MAP[a], mean ± SD, mmHg	81.9 ± 11.4	79.0 ± 10.0	<0.001	79.6 ± 9.7	79.1 ± 10.0	5.4
Laboratory parameters[b]						
HGB, mean ± SD, g/dl	10.9 ± 2.3	10.7 ± 2.3	0.081	10.7 ± 2.3	10.7 ± 2.3	1.6
PLT, median (IQR), K/uL	210 (154–252)	182.5 (138–224.5)	<0.001	184 (136–219)	184 (136–225)	4.3
WBC, median (IQR), K/uL	10.5 (7.5–14.4)	11.7 (8.3–15.5)	0.002	12.8 (8.7–15.4)	12.7 (8.2–15.4)	1.9
Scr, median (IQR), mg/dl	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.299	0.9 (0.7–1.2)	0.90 (0.7–1.2)	7.5
Comorbidity[e], n (%)						
Myocardial infarction	516 (14.4%)	60 (16.7%)	0.252	68 (19.3%)	58 (16.4%)	7.8
Cerebrovascular disease	602 (16.8%)	48 (13.3%)	0.088	50 (14.2%)	47 (13.3%)	2.4
Chronic kidney disease	616 (17.2%)	45 (12.5%)	0.022	52 (14.7%)	45 (12.8%)	5.6
Severe liver disease	176 (4.9%)	18 (5.0%)	0.948	16 (4.5%)	18 (5.1%)	2.6
Malignant cancer	375 (10.5%)	22 (6.1%)	0.009	16 (4.5%)	22 (6.2%)	6.2
Diabetes	1045 (29.2%)	94 (26.1%)	0.215	105 (29.7%)	93 (26.3%)	7.6
Hypertension	476 (13.3%)	39 (10.8%)	0.184	31 (8.8%)	39 (11.0%)	7.0
Sepsis	1586 (44.4%)	210 (58.3%)	<0.001	213 (60.3%)	207 (58.6%)	3.4
ARDS	76 (2.1%)	11 (3.1%)	0.252	8 (2.3%)	11 (3.1%)	5.3
Delirium, n (%)	964 (27.0%)	219 (60.8%)	<0.001	213 (60.3%)	212 (60.1%)	0.6
RRT, n (%)	212 (5.9%)	17 (4.7%)	0.351	19 (5.4%)	17 (4.8%)	2.5
Mechanical Ventilation, n (%)	1155 (32.3%)	295 (81.9%)	<0.001	294 (83.3%)	288 (81.6%)	4.0
Vasopressors use, n (%)	636 (17.8%)	132 (36.7%)	<0.001	130 (36.8%)	127 (36.0%)	2.0
GCS[c], median (IQR)	15 (14–15)	15 (13–15)	0.092	15 (13–15)	15 (13–15)	2.7
SOFA score[d], median (IQR)	3 (1–5)	5 (3–8)	<0.001	5 (3–8)	5 (3–8)	2.6
Antidepressant, n (%)	2047 (57.2%)	185 (51.4%)	0.033	187 (53.0%)	184 (52.1%)	1.7
Propofol[f], n (%)	973 (27.2%)	295 (81.9%)	<0.001	292 (82.7%)	288 (81.6%)	2.7
Midazolam[g], n (%)	262 (7.3%)	71 (19.7%)	<0.001	51 (14.4%)	68 (19.3%)	14.3

Abbreviations: MAP mean arterial pressure; HGB hemoglobin; PLT platelet; WBC white blood cell; Scr serum creatinine; ARDS acute respiratory distress syndrome; RRT renal replacement therapy; SOFA sequential organ failure assessment; GCS Glasgow Coma Scale.
[abcd]The first values during the first day after ICU admission were recorded
[e]Comorbidities were assessed with the Charlson Comorbidity Index.
[f]Propofol was defined as propofol use during the first 48h of ICU admission
[g]Midazolam was defined as midazolam use during the first 48h of ICU admission
Propensity matching by male, age, weight, mean blood pressure, PLT, serum creatinine, SOFA score, chronic kidney disease, severe liver disease, malignant cancer, sepsis, delirium, mechanical ventilation, vasopressors, RRT, antidepressant, propofol, midazolam

Relationship between dexmedetomidine and outcomes

Before PSM, no significant difference was found regarding 30-day mortality and in-hospital mortality (Table 2). Patients in the dexmedetomidine group were more likely to have an increased length of ICU stay [dexmedetomidine: 3.2 (2.0–6.3), non-dexmedetomidine: 1.9 (1.1–3.8)]. AS shown in Table 3, multivariable logistic regression analysis, adjusted for multiple potential confounders, demonstrated that dexmedetomidine use was associated with a reduction in in-hospital mortality (OR = 0.451; 95% CI 0.270–0.754; P = 0.002). Cox regression analysis showed that dexmedetomidine use was significantly associated with lower 30-day mortality after ICU admission (HR = 0.673, 95% CI 0.459–0.987, P = 0.043). Multivariable linear regression analysis revealed no statistically significant association between dexmedetomidine use and the length of ICU stay (P > 0.05). In the overlap weighting analysis, early dexmedetomidine use was associated with lower in-hospital mortality (OR = 0.535, 95% CI: 0.328–0.872,

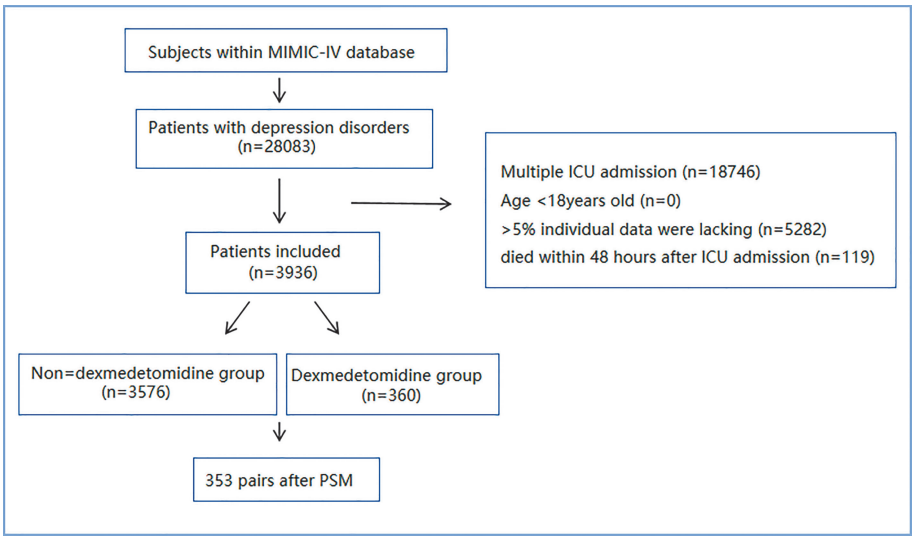

Fig.1 Flowchart of Included Patients.

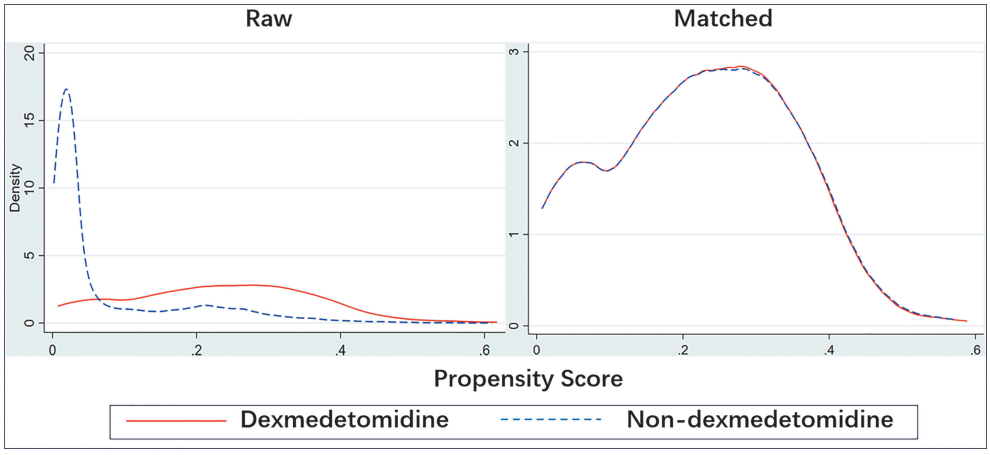

Fig.2 Propensity score distribution plots before and after PS-matching

P = 0.012). However, the association with 30-day mortality did not reach statistical significance (HR = 0.703, 95% CI: 0.480–1.028, P = 0.069). In sensitivity analyses excluding patients in the initial non-dexmedetomidine group who subsequently received dexmedetomidine after 48 hours of ICU admission, early dexmedetomidine use remained significantly associated with lower 30-day mortality (HR = 0.573, 95% CI: 0.383–0.857, P = 0.007). Similarly, dexmedetomidine use was associated with lower in-hospital mortality (OR = 0.479, 95% CI: 0.285–0.806, P = 0.006).

After PSM, 353 patients receiving dexmedetomidine were successfully matched with 353 patients not receiving dexmedetomidine. As shown in Table 1, the matched groups had well-balanced baseline characteristics, with most covariates showing standardized mean differences (SMDs) below 10%. After matching, the dexmedetomidine group had significantly lower in-hospital mortality (5.9% vs. 12.5%) and 30-day mortality (9.3% vs. 15.6%), while there was no statistically significant difference in the duration of ICU stay between the two groups (P > 0.05) (Table 2). Consistent with the pre-matching model, dexmedetomidine use remained significantly associated with reduced in-hospital mortality (OR = 0.465, 95% CI 0.274–0.791, P = 0.005). After PSM, multivariable Cox regression showed that early dexmedetomidine use was independently associated with lower 30-day mortality (HR = 0.577, 95% CI: 0.371–0.898, P = 0.015). The proportional hazards assumption of the Cox model was evaluated using Schoenfeld

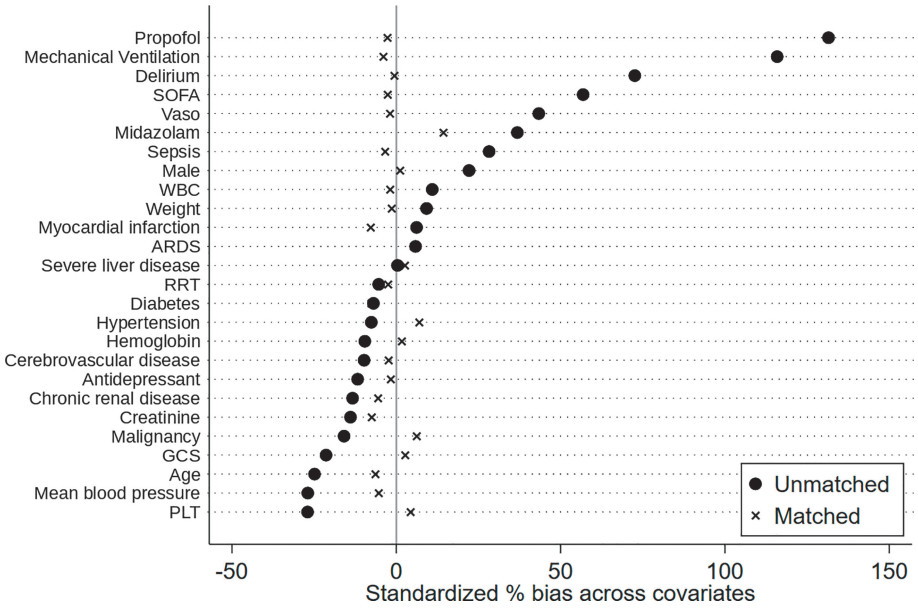

Fig.3 Love plot showing the standardized mean difference before and after PS-matching. Abbreviations: Vaso vasopressor; PLT platelet; WBC white blood cell; ARDS acute respiratory distress syndrome; RRT renal replacement therapy; SOFA sequential organ failure assessment; GCS Glasgow Coma Scale.

Table 2 Outcomes between Dexmedetomidine group and Non-dexmedetomidine group

Outcomes	Unmatched patients		P	Propensity-score-matched patients		P
	Non-Dexmedetomidine n = 3576	Dexmedetomidine n = 360		Non-Dexmedetomidine n = 353	Dexmedetomidine n = 353	
In-hospital mortality, n (%)	235 (6.6%)	21 (5.8%)	0.588	44 (12.5%)	21 (5.9%)	0.003
30-day mortality, n (%)	336 (9.4%)	33 (9.2%)	0.887	55 (15.6%)	33 (9.3%)	0.012
ICU time, median (IQR), days	1.9 (1.1-3.8)	3.2 (2.0–6.3)	<0.001	2.8 (1.6–6.6)	3.2 (2.0–6.1)	0.610

Table 3 Association between dexmedetomidine administration and clinical outcomes in critically ill patients with depression

	In-hospital mortality[a]		30-day mortality[b]		ICU time[c]	
	OR (95% CI)	P	HR (95% CI)	P	B (95% CI)	P
Pre–matched cohort (n = 3936)	0.451 (0.270–0.754)	0.002	0.673 (0.459–0.987)	0.043	0.204 (–0.459 –0.868)	0.545
Post–matched cohort (n = 706)	0.465 (0.274–0.791)	0.005	0.577 (0.371–0.898)	0.015	0.237 (–0.690–1.164)	0.615

[a]Impact of dexmedetomidine use on the In-hospital mortality was estimated with multivariable logistic regression model using backward elimination, based on P value <0.1, including age, platelet, cerebrovascular disease, severe liver disease, malignant cancer, ARDS, RRT, SOFA score, vasopressors use, Sepsis, Mechanical ventilation, delirium.
[b]Cox regression was used for estimating the impact of dexmedetomidine use backward elimination, based on P value <0.1, including age, cerebrovascular disease, severe liver disease, malignant cancer, ARDS, chronic kidney disease, SOFA score, vasopressors use, Sepsis, Mechanical ventilation, delirium.
[c]Linear regression was used to evaluate the association between dexmedetomidine use and length of ICU stay. HR was calculated using the formula $HR = e^{\beta i}$.
Note: For the matched cohort, Cox model assumptions were validated by Schoenfeld residuals (dexmedetomidine P = 0.887). Sensitivity analysis for unmeasured confounding yielded E-values (point estimate: 2.86; lower CI limit: 1.47).

residuals. Both the global test and individual variable tests indicated no substantial violation of the assumption for the primary exposure of interest (P = 0.887 for dexmedetomidine). The E-value for the point estimate was 2.86, and the E-value for the CI limit was 1.47 (Table 3). No statistically significant association was shown in the multivariable linear regression analysis (Table 3). Kaplan-Meier curve analysis confirmed the association between dexmedetomidine use and reduced 30-day mortality (P = 0.0113) (Fig. 4).

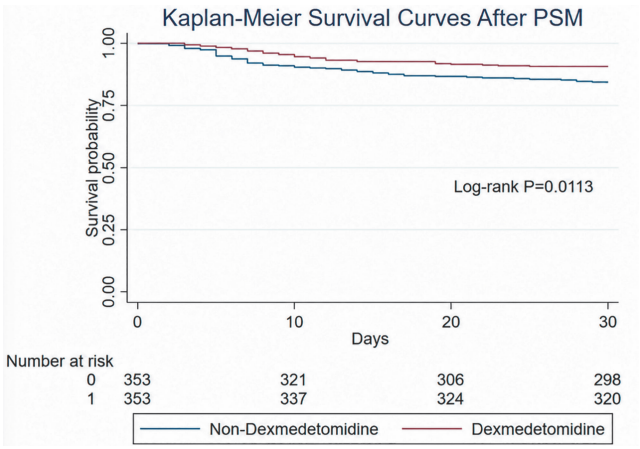

Fig.4 Kaplan-Meier method estimated 30-day mortality in ICU patients with depression disorder stratified by dexmedetomidine after propensity score matching

Subgroup analysis

Subgroup analyses were performed in Figure 5, stratified by age, SOFA, GCS, Sepsis status, delirium status, mechanical ventilation use and antidepressant use during hospitalization after propensity score matching (Fig. 5). Patient numbers within each subgroup are displayed in the corresponding figure. In the adjusted model, there was no significant interaction found in the subgroup analysis. The association between dexmedetomidine use and lower 30-day mortality was statistically significant in the subgroup without sepsis (HR 0.309, 95% CI 0.097–0.985), with GCS = 15 (HR 0.460, 95% CI 0.246–0.860) and the subgroup with mechanical ventilation (HR 0.585, 95% CI 0.372–0.922). In the subgroup analysis, the association between dexmedetomidine use and 30-day mortality was consistent regardless of antidepressant use (P for interaction = 0.179). Specifically, the HR for patients using antidepressants was 0.779 (95% CI: 0.414–1.466, P = 0.439), compared to 0.435 (95% CI: 0.240-0.788, P = 0.006) in the non-user group. HR for patients with delirium was 0.549 (95% CI: 0.339–0.887, P = 0.014), compared to 0.730 (95% CI: 0.249–2.141, P = 0.566) in those without delirium. No significant interaction was observed between delirium status and dexmedetomidine efficacy (P = 0.634).

Discussion

This study investigates the association between early dexmedetomidine administration and short-term outcomes in ICU patients with comorbid depression. After adjusting for confounding factors, our findings demonstrate a significant association between early dexmedetomidine use and lower in-hospital as well as 30-day mortality. These

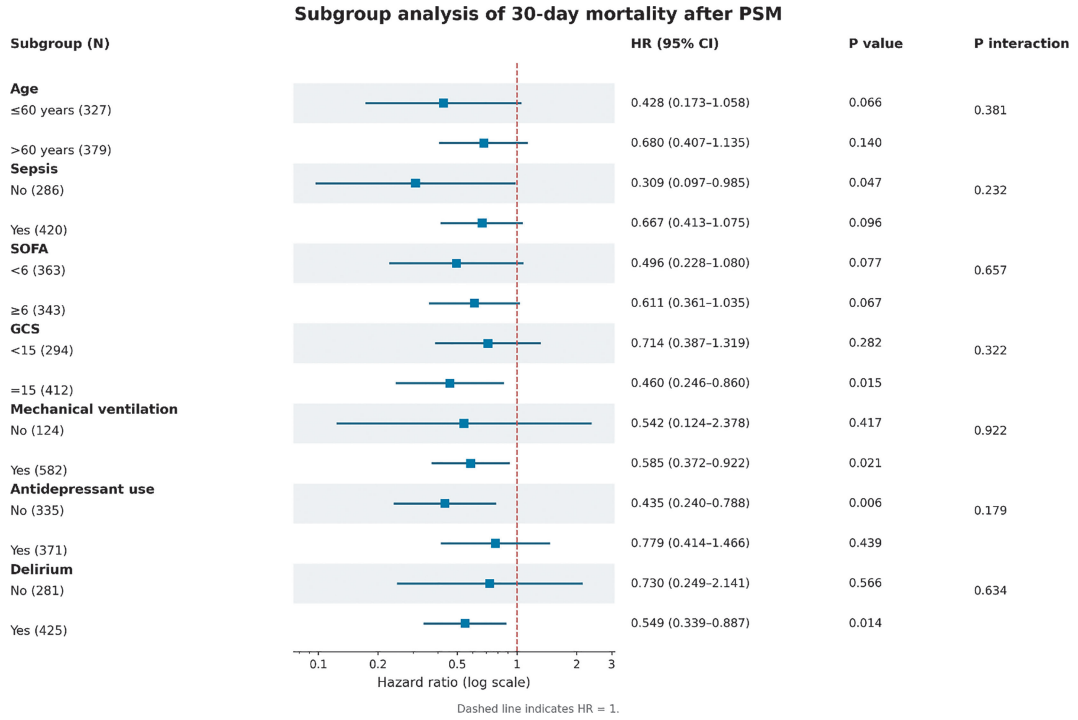

Fig.5 The association between dexmedetomidine and 30-day mortality in subgroups after propensity score matching.

results suggest a potential therapeutic link that has been largely unexplored in previous studies concerning this specific psychiatric population.

Depressive disorders are polymorphic mood disorders caused by interacting psychosocial, genetic, and neurobiological factors, which manifest in diverse symptoms. They are also strongly connected with suicidal ideation, self-harm, attempted and completed suicide. Patients in the ICU often require circulatory and respiratory support. These invasive therapies, along with the ICU environment, frequently induce pain, insomnia, anxiety, and other discomforts, which may complicate the clinical course of patients with pre-existing depression. Consequently, optimal sedation is crucial to improve patient tolerance and safety. Based on its unique pharmacodynamic profile and preclinical evidence (including its antidepressive effect and organ-protective effect), dexmedetomidine has been hypothesized to offer potential benefits. However, its specific clinical utility in the context of ICU patients with depressive disorders remains to be fully elucidated.

Emerging data highlight the pleiotropic protective effects of dexmedetomidine across various organ systems. In animal models, beyond its known neuroprotective role against ischemia-reperfusion injuries[12,13], dexmedetomidine has been shown to alleviate myocardial damage caused by sepsis through modulating autophagy and inhibiting inflammation[14]. Moreover, other research has provided evidence for the protective effect of dexmedetomidine in mitigating renal injury among patients after surgery[15,16]. Our findings suggest a potential clinical benefit of dexmedetomidine among ICU patients with depressive disorder, an improvement that may be partially ascribed to its systemic organ-protective effect. However, the clinical effects of dexmedetomidine vary among different patients. While it improved outcomes in elderly in ICU[17] and post-cardiac-surgery patients[18], it did not offer additional benefit over propofol in septic patients requiring mechanical ventilation[19]. Such marked heterogeneity necessitates a context-specific approach to sedation. Identifying the specific patient phenotypes and pathophysiological states most responsive to dexmedetomidine is essential for advancing precision sedation.

Subgroup analyses demonstrated that the inverse association between dexmedetomidine use and 30-day mortality was largely consistent across various clinical strata, including age, SOFA scores, and mechanical ventilation status. The absence of significant interaction (all P for interaction >0.05) suggests that the potential survival advantage observed in patients with depression may not be heavily modified by these baseline factors. Although statistically significant associations were observed among patients without sepsis, those with a GCS score of 15, patients receiving mechanical ventilation, those not receiving antidepressants, and patients with delirium, these findings should be interpreted cautiously. In particular, the association observed in patients receiving mechanical ventilation may be of clinical interest, as dexmedetomidine's sympatholytic properties could potentially be relevant in critically ill patients with increased physiological stress. However, the absence of significant interaction does not support a differential treatment association between patients with and without mechanical ventilation. Notably, the association between dexmedetomidine use and lower mortality was observed among patients with delirium, whereas no significant association was detected among those without delirium. Nevertheless, the interaction test was not statistically significant (P for interaction = 0.634). Therefore, the observed association may not be entirely explained by differences in delirium status. Given the observational nature of this study, these findings should be interpreted cautiously and require further validation in prospective studies.

Preexisting depression has been identified as an independent factor associated with poor clinical outcomes[3,20], while the exact biological mechanisms remain to be fully elucidated, the association observed in our study may be linked to the unique pharmacological profile of dexmedetomidine. Unlike conventional sedatives, dexmedetomidine possesses distinct anxiolytic and antidepressant-like properties, as suggested by its ability to reduce the incidence of postpartum depression[9]. Animal studies further support dexmedetomidine's potential in alleviating depressive and anxiety-like behaviors under conditions of sleep deprivation and stress[5,21]. Moreover, patients with depression may be more susceptible to post-intensive care syndrome (PICS), characterized by physical, cognitive, and mental impairments after critical illness[22]. Clinical evidence suggests that nocturnal dexmedetomidine use is associated with lower incidence of PICS, particularly in reducing psychological impairment[23]. Furthermore, its ability to improve sleep quality[24-26] may specifically address the disturbances common in depressed patients. Consequently, the association between dexmedetomidine and the improved short-term outcomes may be partly explained by its multitarget effects against anxiety, depression, and sleep disruption, which could help mitigate the psychological burden of critical illness.

Limitation

Our study has several limitations. First, the relatively small number of dexmedetomidine users and the heterogeneous

sedation strategies in the non-dexmedetomidine group limited our ability to distinguish the independent effects of different sedatives. Despite propensity score matching and overlap weighting, residual confounding by indication cannot be excluded. Second, the MIMIC-IV database lacks detailed information on depression severity, duration, and psychiatric history, limiting the characterization of the study population. Third, dexmedetomidine exposure was defined within the first 48 hours after ICU admission, and patients who died within this period were excluded to reduce potential immortal time bias. Nevertheless, residual time-related bias cannot be completely ruled out. In addition, delirium and concomitant sedative use were assessed during the same 48-hour period, and their temporal relationships with dexmedetomidine administration could not be clearly established. Therefore, potential overadjustment bias cannot be excluded. Fourth, we did not systematically evaluate dexmedetomidine dosage, infusion duration, or potential adverse events, such as bradycardia and hypotension. Given the complexity of critical illness and concomitant treatments, these aspects warrant further investigation in future studies. Finally, the observational nature of this study limits causal interpretation, and the findings should be interpreted as associations rather than evidence of a causal effect. Further large-scale, multicenter prospective studies are needed to validate our findings.

Conclusion

Early dexmedetomidine administration as a sedative therapy for ICU patients with comorbid depression is significantly associated with lower in-hospital mortality and 30-day mortality. While these findings suggest that dexmedetomidine may be a favorable sedation option for this population, further randomized controlled trials are needed to confirm these observed associations.

Abbreviations

MIMIC-IV: Medical Information Mart for Intensive Care-IV; PSM: Propensity score matching; ICU: Intensive care unit; BIDMC: Beth Israel Deaconess Medical Center; IRBs: Institutional Review Boards; MIT: Massachusetts Institute of Technology; SOFA: Sequential Organ Failure Assessment; MAP: Mean arterial pressure; ICD: International Classification of Diseases; RRT: Renal replacement therapy; IQR: Interquartile range; SMD: Standardized mean difference; GCS: Glasgow Coma Scale; SD: Standard Deviation; HGB: hemoglobin; PLT: platelet; WBC: white blood cell; Scr: serum creatinine; ARDS: acute respiratory distress syndrome; SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin and Norepinephrine Reuptake Inhibitors; TCA: Tricyclic Antidepressants; PICS: post-intensive care syndrome; CAM-ICU: Confusion Assessment Method for the ICU assessment; RASS: Richmond Agitation-Sedation Scale score.

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Availability of data and materials

The datasets analyzed in this study are available in the MIMIC-IV repository on PhysioNet (https://physionet.org/). Access is restricted to credentialed users who meet the platform's ethics training and data use requirements.

Consent for publication

Not applicable. All data in the MIMIC database were fully anonymized prior to analysis, and this manuscript does not contain any individual person's identifiable data in any form.

Ethics approval and consent to participate

MIMIC IV database used in the present study was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology and does not contain protected health information.

Competing interests

The authors declare that they have no competing interests.

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